Meeting Today's Challenges: The Evolving Role of the IBC

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Outline

- New areas of Research and Biosafety Issues
- Framework for oversight: local & federal
- NIH Guidelines & NIH
- Responsibilities of the institution
- Institutional Biosafety Committee : general and specific (HGT trials)
- Responsibility of the investigator

Recent Changes: Role of IBC

- Human Gene Transfer Research
- Serious Adverse Event Reporting
- Review and Oversight of Human Xenotransplantation Research
- Review and Oversight of Select Agent Research
- Coming soon, Dual Use

Framework for Oversight

- **Federal (many agencies)**
  - **NIH**
  - **DoD**
  - **FDA**
  - **OHRP**
  - **OLAW**
  - CDC
  - **USDA/APHIS**
  - **DOJ/FBI**

- **Local (many layers)**
  - **Provost, VP Research**
  - **Sponsored Programs**
  - **IRB**
  - **IBC**
  - **IACUC**
  - **Investigator**

Recent NIH Initiatives

- Public access to SAE reports,harmonization of definition and timing with the FDA
- Establishment of GTSAB
- Revision of HGT Protocol review process
- Development of GTPC
- Long term patient follow up

Recent NIH Initiatives

- Changes to RG classifications for certain viral and bacterial agents.
- Guidance on Ad vector use
- Development of GEMCRIS
- NIH effort on IBC professional development

NIH Guidelines for Research Involving Recombinant DNA Molecules

Amendment Effective July 28, 1994, Federal Register, August 5, 1994 (59 FR 40170)
Amendment Effective April 17, 1995, Federal Register, April 27, 1995 (60 FR 20726)
Amendment Effective December 14, 1995, Federal Register, January 19, 1996 (61 FR 1482)
Amendment Effective March 1, 1996, Federal Register, March 12, 1996 (61 FR 10004)
Amendment Effective January 23, 1997, Federal Register, January 31, 1997 (62 FR 4782)
Amendment Effective September 30, 1997, Federal Register, October 14, 1997 (62 FR 53335)
Amendment Effective October 20, 1997, Federal Register, October 29, 1997 (62 FR 56196)
Amendment Effective October 22, 1997, Federal Register, October 31, 1997 (62 FR 59032)
Amendment Effective February 4, 1998, Federal Register, February 17, 1998 (63 FR 8052)
Amendment Effective April 30, 1998, Federal Register, May 11, 1998 (63 FR 26018)
Amendment Effective April 29, 1999, Federal Register, May 11, 1999 (64 FR 25361)
Amendment Effective October 2, 2000, Federal Register, October 10, 2000 (65 FR 60328)
Amendment Effective December 28, 2000 Federal Register, January 5, 2001 (66 FR 1146)
Amendment Effective December 11, 2001 Federal Register, December 11, 2001 (66 FR 64051)
Amendment Effective December 19, 2001 Federal Register, November 19, 2001 (66 FR 57970)
Amendment Effective January 10, 2002 Federal Register, December 11, 2001 (66 FR 64052)
Amendment Effective January 24, 2002 Federal Register, November 19, 2001 (66 FR 57970)

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)

April 2002

Visit the OBA Web site at:
http://www4.od.nih.gov/oba
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and Information about upcoming Gene Therapy Policy Conferences

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

These *NIH Guidelines* supersede all earlier versions and shall be in effect until further notice.

TABLE OF CONTENTS

SECTION I SCOPE OF THE *NIH GUIDELINES* 8
Section I-A. Purpose 8
Section I-B. Definition of Recombinant DNA Molecules 9
Section I-C. General Applicability 9
Section I-D. Compliance with the *NIH Guidelines* 10
Section I-E. General Definitions 10

http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

NIH Guidelines

- Review process necessary for various types of rDNA research
- Physical and biological containment
- Responsibilities of the institutions, investigators, IBCs ,BSO, and NIH
- Points to Consider in design..Appendix M

NIH Guidelines: Apply to

- Recombinant DNA research that is
  - Funded by the NIH
  - Performed at or sponsored by an institution that receives any NIH funding for rDNA research
- Rational: For Biosafety to be meaningful it has to be observed by all investigators at an institution

NIH Guidelines

- “Guidelines” does not mean optional
- Compliance with the NIH Guidelines are a term and condition of NIH funding for recombinant DNA research

Why Comply with the NIH Guidelines?

- Funding
- NIH Guidelines are recognized by all other federal agencies
- Become the “Recognized Standard for Responsible Oversight”
- Are perceived as the baseline,cannot fall below but can do more

Why Comply with the NIH Guidelines

- Increased institutional awareness and knowledge
- Sharing of resources, collaboration
- Increased safety
- Accident prevention
- Public and community perception
- Community asset and resource

Approval or registration	Oversight level 1	Oversight level 2	Oversight level 3	Oversight level 4	Oversight level 5	Oversight level 6
IBC		initiate simultaneous with notification	approval before initiation	approval	approval	approval
IRB				approval		
NIH OBA			Restricted agents, OBA sets containment, register protocols	registration	registration	submit for review
RAC Review				significant	working group review*	review
NIH Director's Office						approval
Exempt	From NIH oversight					
Section in Guidelines	III-F	III-E	III-D	III-C	III- B	III-A,
Description of section	No hazard, natural exchangers, ex vivo or genes from organelles	Non-pathogenic lower eukaryotes or prokaryotes	Use of various risk group agents as vectors or as donors or recipients	Human gene transfer expts	Cloning of toxin genes	Transfer of drug resistance genes that might compromise control of agent

What do the NIH Guidelines say you must do?

The IBC: Peer and Public review of research, risks, controls and ethics

NIH Guidelines Prescription vs. Flexibility

- Some matters are left to institutional discretion
- Flexibility
  - Accommodates institutional diversity and heterogeneity
  - Can create uncertainty about expectations

Prescription vs. Flexibility

- Need for IBC
- Outside members
- Minimum size
- Expertise
- Annual reporting
- IBC registration
- Compliance for Grants
- Responsibilities
- Frequency of meeting
- Information tracked
- Review process
- Responsibility for other types of research
- Non-institutional members
- Ask for assessment
- Submit data

IBC Registration with NIH

- Assurance of local review of biosafety risks
- Assurance of expertise in review consistent with NIH Guidelines
- Institutional contacts
- Provides a census of the field: where rDNA research done and types

Roles and Responsibilites

Institution, IBC, and PI

Institutional Responsibilities

- Establish an Institutional Biosafety Committee with appropriate expertise
- A Biosafety Officer must be a member of the IBC for Large Scale, BL3 or >
- Ensure appropriate training for IBC members and staff, PIs, laboratory staff

Institutional Responsibilities

- Assist and ensure compliance with Guidelines by investigators
- Establish & maintain health surveillance program
- Report significant problems or violations to OBA within 30 days
- Establish and implement policies for the safe conduct of rDNA research

Role of the Institutional Biosafety Committee

balancing risk/protection

and

scientific quality

Role of the Institutional Biosafety Committee

- Reflection of the responsibility of the institution to ensure the safe conduct of biological research
- Provide a mechanism for public scrutiny of and access to biological research
- minimally driven by specific research or funding source

Scope of the IBC

- Recombinant DNA technologies in the laboratory
- Use of rDNA in animals, e.g., transgenics, knockouts and SiRNA
- Use of rDNA in humans, gene transfer studies and recombinant vaccines

IBC and IACUC Overlap

- Use of biological agents in animals
- Use of carcinogens, cytokines, toxins, etc.
- Generation of transgenic animals
  - Knock in and knock out
  - Viral vectors, naked DNA, plasmid
- Immune compromised animals
- Vaccine development

Comparison of Local Oversight Roles

Committee (agency)	Isolation of gene	In vitro studies	In vivo testing (animal)	Development of animal model	Preclinical studies (murine, primate)	HGT & Xeno clinical trial
IBC (NIH)	+	+	+	+	+	+
IACUC (OLAW)	-	-	+	+	+	-
IRB (OHRP)	-	-	-	-	-	+

The IBC Can Be

- Not just rDNA but drugs, toxins, infectious agents, animal studies, vaccines, xenotransplantation
- An “early warning system”
- Identification of appropriate pre-clinical studies
- Assessment of pre-clinical data in a clinical trial application

Fulfilling the Intent

- IBCs are encouraged to open meetings to public, but not required
- IBC minutes available to public upon request, but confidential/commercial info
- IBC meetings interactive:face to face
- Periodic review (protocol load) annual review is desirable.

IBC Policies and Procedures

- Common problems can give common goals
- Inclusive partnership
- Scientific rationale essential
- Consensus

Investigator or PI

- Responsible for full compliance with NIH Guidelines (not just for HGT trials but for all biological research that involves rDNA
- Receive IBC approval to conduct research, submit descriptions of research & amendments (see section IV-B-7-a-1)
- Ensure adequate training for students & staff

Investigator

- Adhere to IBC approved emergency plans for spills & accidents
- Comply with shipping requirements for rDNA materials
- Fulfill responsibilities to NIH OBA (ask your Biosafety Officer for help)

IRB, IACUC, IBC Overlapping Responsibilities

- Human Gene Therapy
- Xenotransplantation
- Transgenic Animals
- Select Agents & Toxins

Human Gene Transfer Studies

HGT Clinical Trials: Unique

- Age of participants: a reversal of the normal process
- Severity of the underlying illness
- Complexity of therapeutic “drug” and safety issues
- Potential for long term effects
- Need for collaboration IBC, IRB, IACUC

Strategies in Gene Therapy

- gene replacement and/or supplementation
- enhancement of immune function
- immunization
- “suicide” genes
- augment conventional therapies

Scientific Issues in Gene Transfer

vector safety

cell & tissue specificity

transgene expression & regulation

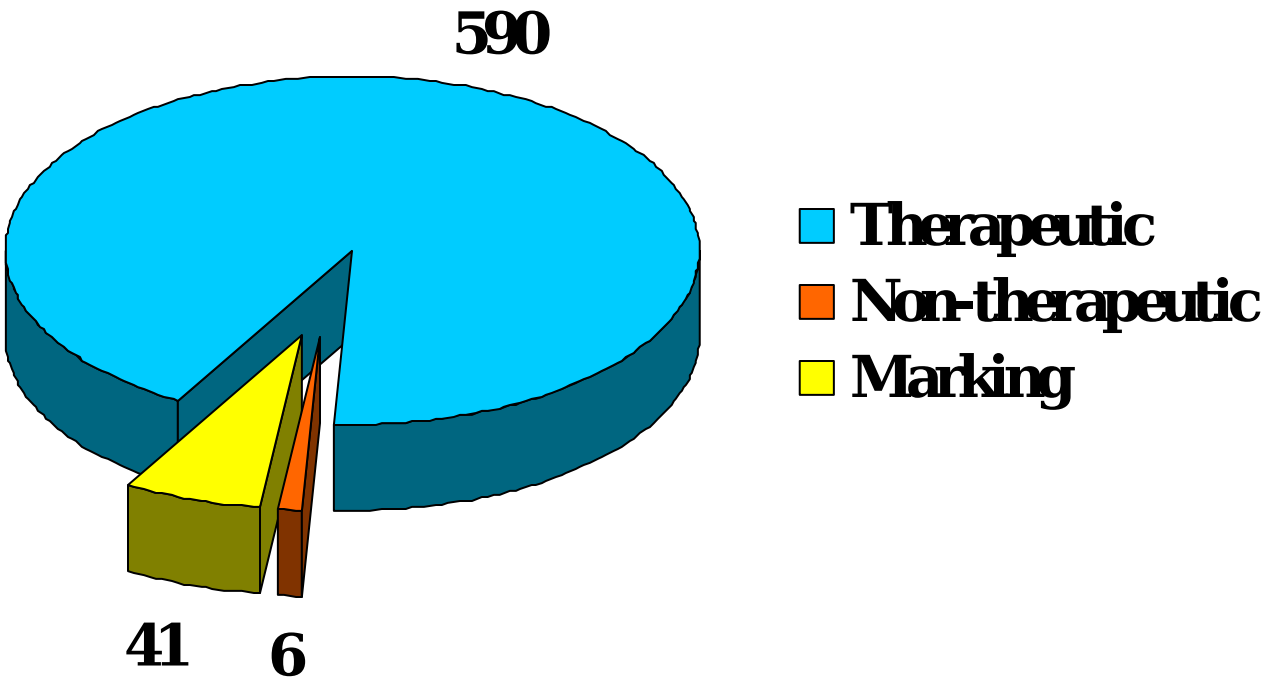
secondary effects of insertion & expression

shedding & exposure of non-patients

Genotype/phenotype correlation

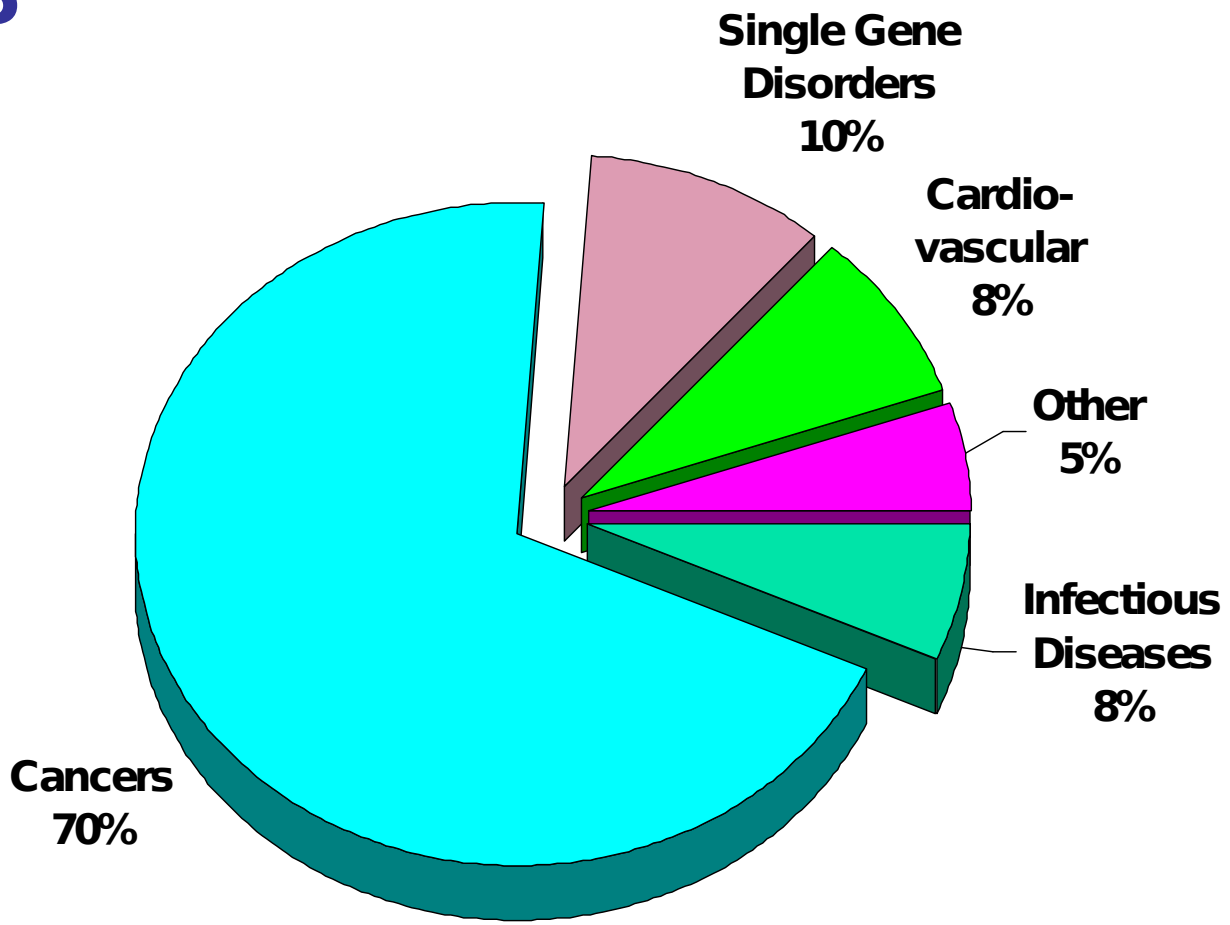
long term effects of gene transfer

Gene Therapy Clinical Trials



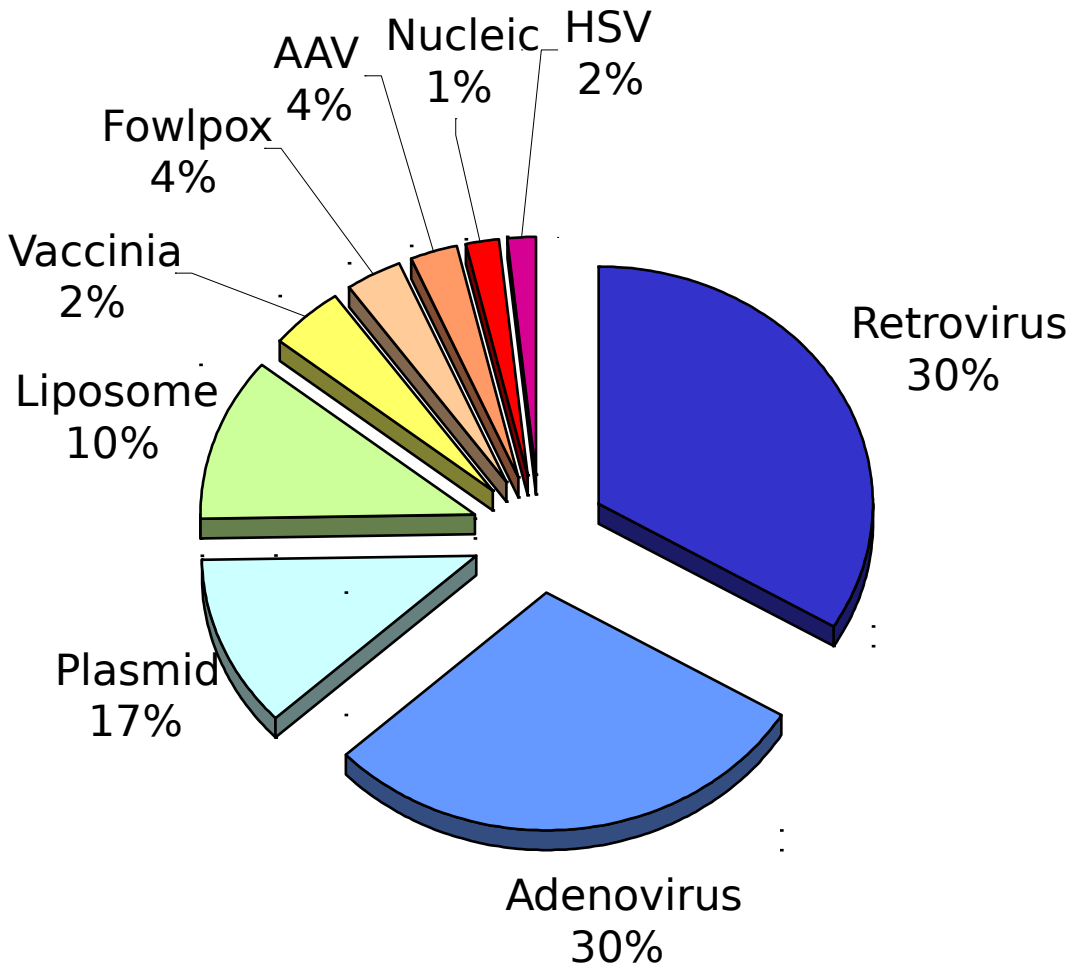
Gene Therapy Trials By Clinical Indication

n =635

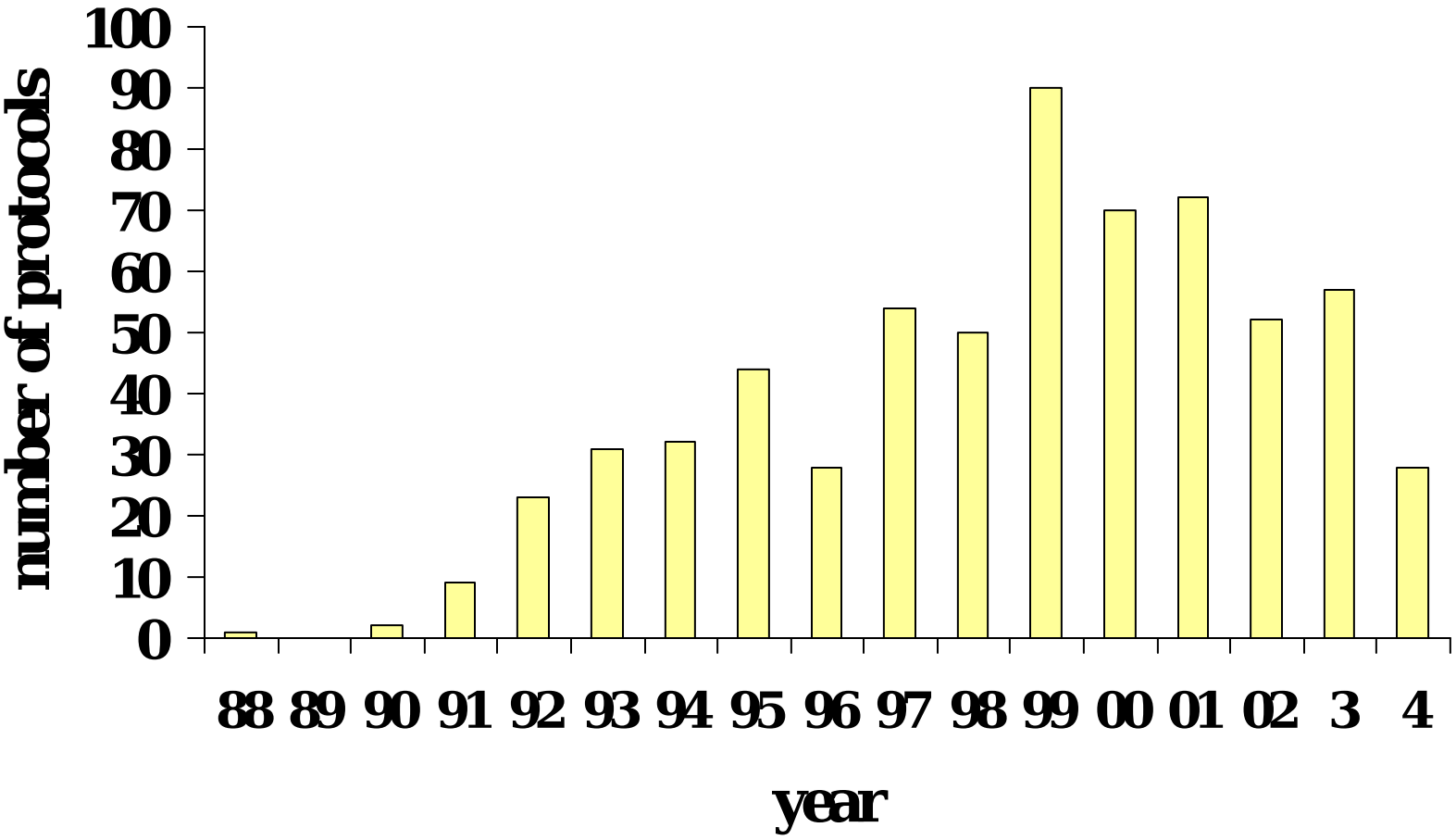


Rev: 3/16/04-ts

Gene Therapy Trials by Delivery Method



Clinical Trials Submitted per Year



Gene Therapy Trials by Phase

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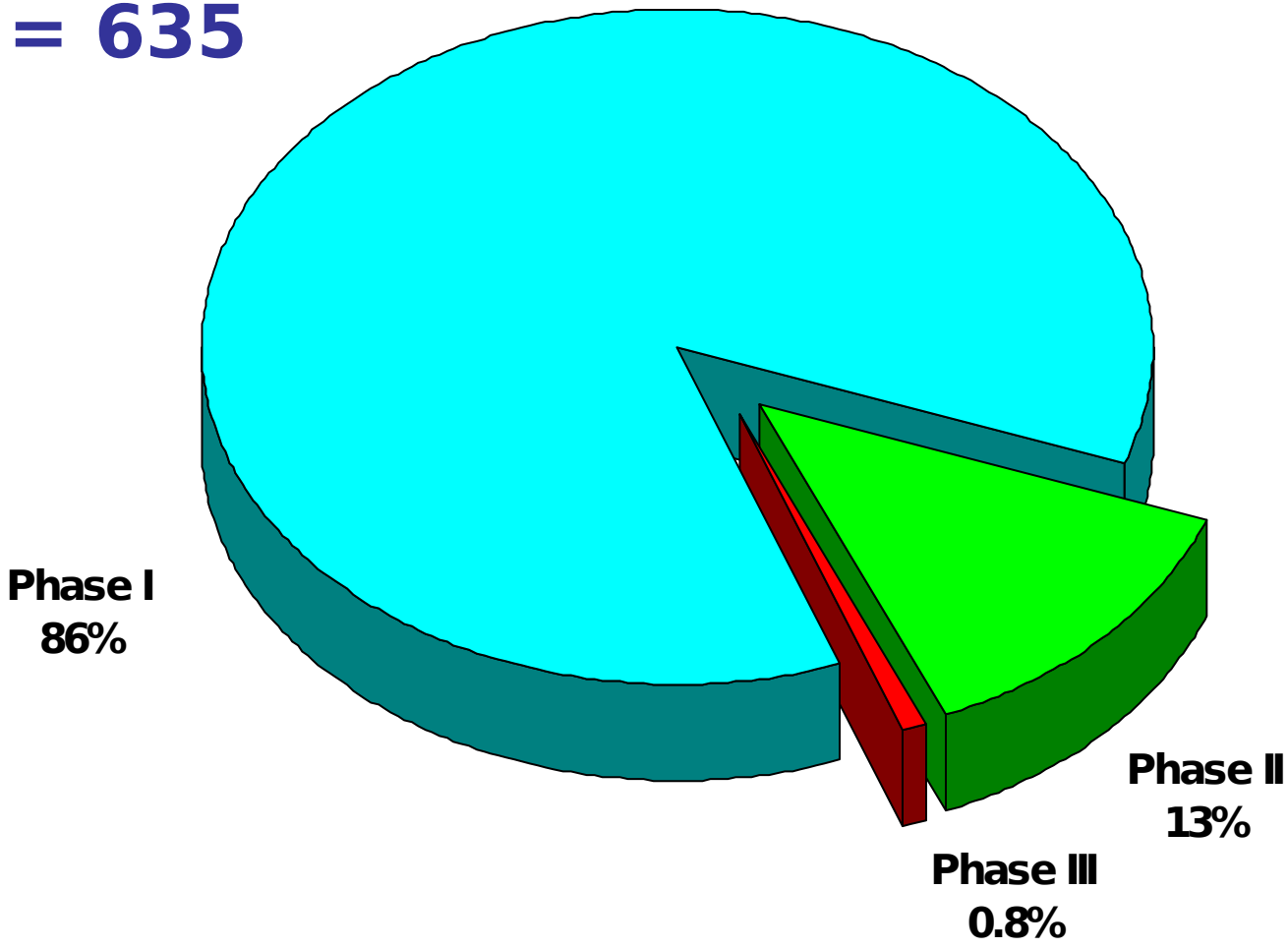


Rev: 3/16/04-ts

The Role of the IBC in HGT

- Scientific quality of protocol, does the preclinical data support the initiation of a human trial as the next logical most reasonable step
- Does the preclinical animal data address and resolve as many safety issues as feasible (are tests in more than one species needed)
- Is the patient monitoring program sufficient, consistent,
- Will/can meaningful data be acquired

Preclinical Studies

adequate model of disease

safety and efficacy in vivo

test of construct

biodistribution, toxicity, secondary effects

Identification of possible surrogate end points: quantitative measures

Proof of concept

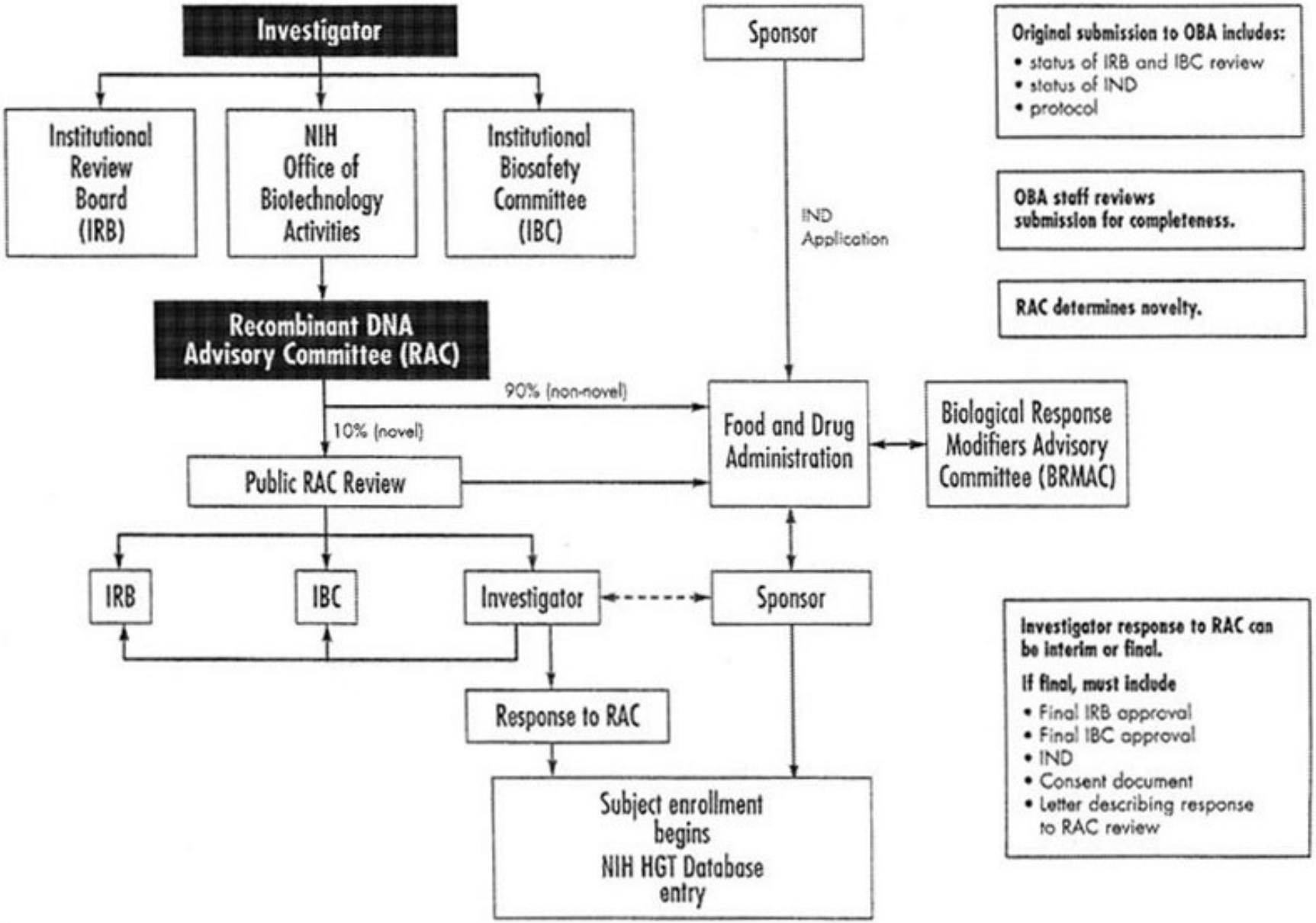
Clinical Trial Review: Risk/ Benefit Assessment

- Potential risks: harm to study participants, close contacts, community
- Potential Benefits: development of therapies for serious/life threatening conditions
- Assessment: do the potential benefits outweigh the potential risks

IBC & IRB Collaboration

- Is the Informed Consent document clear, and adequate, without technical jargon?
- Are preclinical results clearly explained (what they do and do not show)?
- Is information about SAE, outcomes of other trials, other patients presented clearly

NIH Review of Gene Transfer Protocols



Long Term Follow Up

A special issue

Long term risks

- Vector persistance
- Vector integration
- Transgene
- Does the route/mode/dose of administration affect the risk (one death)

Long Term Risks

- Neoplastic
- Hematologic/Immunologic
- Rheumatologic
- Neurologic

What data should be collected and by whom?

- Trials involving gene insertion or gene transfer
- 15 years, first 5 more intense
- Should the data collected by tailored to the trial? Vector? Disease?
- What happens if an adverse event is reported? How do you determine that it is related to the gene transfer product

Who is Responsible for LTFU?

- Investigator
- Sponsor
- Institution
- What if commercial sponsor goes out of business?
- Can this responsibility be transferred to another party?

More Challenges

- What do you say in the informed consent?
  - The risks vary with phase of the study, eg. Study agent vs follow up
  - The risks of procedures vs risks from agent
- If participant withdraws after administration
- If do not agree to long term follow up should participant be excluded?

More Challenges

- Plan for research participants that may lose decision-making capacity over the course of the follow up period? Appoint a research proxy at start?
- Does the HIPPA privacy rule make long term follow up more difficult?
- As new data becomes available how to incorporate results to modify LTFU monitoring?

Initiatives from NIH and FDA

GeMCRIS

Informed Consent assistance

GEMCRIS - Home - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites History Mail Print Edit

Address http://sherlock.resva.trw.com/gemcris10dev/Contents/GC_HOME.asp Go Links

GeMCRIS

Genetic Modification Clinical Research Information System Version 1.0

Home | Public Information | System Help

- Vocabulary Reports
- Protocols by Number
- Protocols by Disease
- Principal Investigators

H OBA Genetic Modification Clinical Research (GeMCRIS) -- Phase II. This system provides l for dissemination of gene transfer clinical research—particularly for Department of Health and Human Services users involved in pre-market reviews of clinical trial data.

Additionally, we are using this Phase II system as a platform for gathering feedback on what other types of information public users would like to see. Please take a moment to respond to a series of questions that appear on a feedback form via the link on this page. Your feedback is critical to the ongoing design of future versions of the product, and it will help us take your needs into consideration as the development of the database continues.

Support

- **Site Map**
- **Frequently Asked Questions**
- **Feedback**
- **Contact Us**

Related Information

- **About RAC**
- **NIH Guidelines**
- **Documents (With Quarterly Reports)**

Site Map

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Done Internet

Key Features of GeMCRIS:

- On-line adverse event reporting to NIH
  - One format for NIH and FDA
- Security measures to protect trade secret and patient confidential information
- On-line search capability
- Implementation of controlled medical vocabularies
- Controlled scientific vocabulary developed specifically for gene transfer research

GeMCRIS: Key Information

- Protocol title
- Study phase
- Clinical indication(s)
- Investigator(s)
- Clinical trial site(s)
- Scientific abstract
- Non-technical abstract
- Investigational strategy
- Vector
- Transgene
- Route of administration

National Institutes of Health
Office of Biotechnology Activities

NIH Guidance on Informed Consent For Gene Transfer Research

Introduction to Guidance

Communication about the Study to Potential Participants

Special Considerations for Informed Consent

- Conflicts of Interest
- Comprehensibility
- Time for Decision Making
- Assent

Consent Form

General Requirements of Human Subjects Research

Specific Requirements of Gene Transfer Research

Appendix M-III-A-2
Comprehensibility

NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

DISCUSSION

Gene transfer research concepts are often difficult for potential participants to understand. Thus, particular care should be given to convey these concepts in the consent form in a readable and understandable manner. Readability and understandability are not synonymous; it is possible to make use of computerized readability scales and still have a consent form that is difficult to understand. Sometimes, reducing reading level without providing additional

TOOLS & BACKGROUND MATERIALS

- Simplification Guide to Medical Terms
- Dartmouth Informed Consent Evaluation Tool
- Written Assessment Tool
- Telephone Evaluation Plan
- FDA Guidance on Non-English Speaking Subjects

MAIN POINTS

- Investigators should be attentive to using language easily read and understood by potential participants.
- Various methods and tools exist to improve and assess comprehension of information.
- All verbal and written

Public Trust = Public access to information*

*Recognizing the need to protect commercially sensitive information, manufacturing, Patents & Trademark

Ethical Dilemmas

Disorder	Alternative Treatment	Efficacy of Alternative	Outcome without Gene Therapy	Outcome with Gene Therapy	Ethical bar
Monogenic disease	No	No	High morbidity & mortality	Alleviation, increased survival	No
Monogenic Disease	Yes	Poor or Low	High morbidity, mortality	Alleviation, increased survival	No
Life - threatening	Yes	Low to fair	Lower survival	Increased survival	No
Serious	Yes	Fair	High morbidity, quality of life low	Decreased morbidity, increased quality of life	Yes and No
Other Disorders, chronic	Yes or No	Good or none	Low to no morbidity, life span within the normal range	Life span within normal range, no morbidity, increased function	Yes

Ethical & Public Issues

Patient Safety & Informed Consent Process

Public access to Serious Adverse Event data

Conflict of Interest, researchers & institutions

in utero Gene Transfer

Germ line Gene Transfer

Enhancement

Goal

Mutually supportive and interactive assessment of risks to participants, families, staff, investigators, and the community

What IBCs face

- Increasingly complex research
- Need for wider range of expertise
- Expanding role of the IBC (unfunded mandates)

The IBC

- What is your process now, can you outline the review and approval process
- How do you meet your regulatory requirements, what steps
- Can the process be improved
- Does the IBC communicate, collaborate with IACUC and IRB

Questions?